Biomolecules & Therapeutics

Review
Biomol Ther 27(3), 265-275 (2019)

Possible Effects of Radiofrequency Electromagnetic Field Exposure on Central Nerve System

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Abstract

Technological advances of mankind, through the development of electrical and communication technologies, have resulted in the exposure to artificial electromagnetic fields (EMF). Technological growth is expected to continue; as such, the amount of EMF exposure will continue to increase steadily. In particular, the use-time of smart phones, that have become a necessity for modern people, is steadily increasing. Social concerns and interest in the impact on the cranial nervous system are increased when considering the area where the mobile phone is used. However, before discussing possible effects of radiofrequency-electromagnetic field (RF-EMF) on the human body, several factors must be investigated about the influence of EMFs at the level of research using *in vitro* or animal models. Scientific studies on the mechanism of biological effects are also required. It has been found that RF-EMF can induce changes in central nervous system nerve cells, including neuronal cell apoptosis, changes in the function of the nerve myelin and ion channels; furthermore, RF-EMF act as a stress source in living creatures. The possible biological effects of RF-EMF exposure have not yet been proven, and there are insufficient data on biological hazards to provide a clear answer to possible health risks. Therefore, it is necessary to study the biological response to RF-EMF in consideration of the comprehensive exposure with regard to the use of various devices by individuals. In this review, we summarize the possible biological effects of RF-EMF exposure.

Key Words: Electromagnetic field, Radiofrequency, Brain, Central nervous system, Stress, Neuron

INTRODUCTION

There is a constant geomagnetic field on the surface of the planet as solar wind generated from the sun meets with the inside of the earth. Therefore, all life on Earth is always living in the presence of an electromagnetic field (EMF) (Hollenbach and Herndon, 2001). With the development of science and technology, artificial electromagnetic waves have been generated on Earth, and the German physicist Heinrich Hertz experimentally discovered electromagnetic radiation and confirmed the existence of the EMF in the ecosystem.

With the progress of science and technology, many electronic devices have been invented and used, therefore, we have easily been exposed to the created artificial electromagnetic waves in our daily life. Especially, explosive use of various electronic devices in modern society has inevitably led to increase continuously the chances of electromagnetic wave exposure. The development of wireless communication technologies, such as computers and smartphones, have become a necessity for modern people. As a consequence, all living things on Earth are experiencing environmental changes and are being exposed to artificial electromagnetic waves which have not been experienced before.

The effect of electromagnetic waves on living creatures has been controversial due to studies with contradicting results. However, in 2011, since the World Health Organization's International Agency for Research on Cancer (IARC) designated mobile phone RF-EMFs as Group 2B, that is, possibly carcinogenic to humans, the social anxiety about electromagnetic exposure has increased (Baan *et al*., 2011). Considering the fact that most people, including young children, use mobile phones in Korea, the possibility of exposure to a considerable amount of electromagnetic waves exists all around us, therefore social interest in the impact on RF-EMF exposure has been greatly increased (Langer *et al*., 2017).

There are many controversies regarding RF-EMF expo-

Open Access https://doi.org/10.4062/biomolther.2018.152

Received Aug 7, 2018 **Revised** Nov 1, 2018 **Accepted** Nov 6, 2018
Published Online Nov 27, 2018

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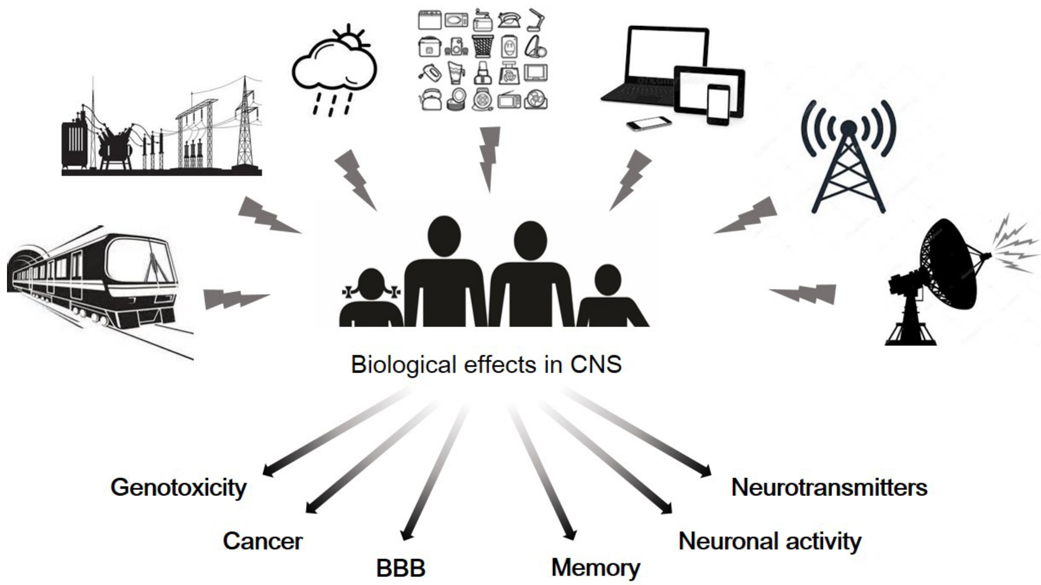

Fig. 1. Schematic summary of the possible biological effects of exposure to EMFs.

sure, but many of the studies have focused on cancer (Morgan *et al*., 2015), genetic damage (Kim *et al*., 2008; Ruediger, 2009), neurological disease (Jiang *et al*., 2016; Kim *et al*., 2017b), reproductive disorders (Falzone *et al*., 2011; Altun *et al*., 2018), immune dysfunction (Kazemi *et al*., 2015; Ohtani *et al*., 2015), kidney damage (Kuybulu *et al*., 2016; Türedi *et al*., 2017), as well as electromagnetic hypersensitivity (Gruber *et al*., 2018), and cognitive effects (Son *et al*., 2018). However, the possible biological effects of exposure to RF-EMF have not yet been proven and there are insufficient data on the biological hazards to provide a clear answer to possible health risks. Thus, the vague fear for the many unknown effects of RF-EMF exposure is expressed as ungrounded negative effects not only to the scientific community but also to the general public. In addition to this, scientific data published by various researchers have been contradictory in their outcome. In particular, detailed information regarding the mechanism of biological effect by RF-EMFs has not yet been elucidated clearly. Recent studies show that RF-EMFs emitted by cellular phones are absorbed into the brain, to a degree, that can affect neuronal activity (Kleinlogel *et al*., 2008; Jeong *et al*., 2015; Jiang *et al*., 2016). In addition, the thermal effects of RF-EMFs suggest the possibility of affecting neuronal activity by temperature generated by mobile phones (Wainwright, 2000; Wyde *et al*., 2018). Therefore, there is a need for scientifically proven information on the effects of increasing exposure to RF-EMFs on nerve cells, including neurodevelopment, function and cognitive functions (Calvente *et al*., 2016; Birks *et al*., 2017). However, many studies on the possible influence of electromagnetic waves on neurons have recently been conducted with great interest, but there are conflicting results according to experimental conditions and there is still much to be studied to gain a basic understanding. Therefore, this paper summarizes the recent studies on the suggested possible biological effects of exposure to RF-EMFs (Fig. 1).

ELECTROMAGNETIC FIELDS IN OUR LIFE

Electromagnetic waves can be classified into Extremely Low Frequency (ELF-EMF), RF-EMF, and Microwave Radiation depending on the wavelength range. Generally, ELF-EMF, frequencies in the range of 3 to 3,000 Hz, are generated from the electronics and electric wires used in homes and workplaces. ELF-EMF is also emitted from the high-voltage power lines that transmit electricity from the power plant to the areas where electricity is used (Barr *et al*., 2000). RF-EMF range from 100 kHz to 300 GHz, which generates an electromagnetic field that propagates through space when a radio frequency current is supplied to an antenna (ICNIRP, 1998; Cucurachi *et al*., 2013). RF-EMF is emitted from devices such as mobile phones, Wi-Fi systems, satellite communication systems, radio, TV stations, and interactive radios. Many of these wireless communication devices are increasingly used in human life (Fig. 2). When using electronic devices (mobile phones, computers, microwave ovens etc.), essentially electromagnetic waves are generated. These waves can be absorbed by human or animal bodies; the specific absorption rate (SAR) is a numerical expression of these absorbed waves. SAR refers to the amount of radio wave energy absorbed in unit mass of human body (1 kg or 1 g); units are W/kg or mW/g. Electromagnetic waves emitted by mobile phones are of high frequency, thus capable of body temperature increase; such heat reactions are expressed quantitatively by SAR. Because RF-EMFs can penetrate into the body and cause vibration of charged or polar molecules inside, it is critical to human health and safety. National Radio Research Agency has released SAR standards of SAR-related international organizations and major countries with related matters. The current emission standard of Republic of Korea for cell phone is 1.6 W/kg averaged over 1 g of tissue but the IEEE and ICNIRP standard are 2.0 W/kg averaged over 10 g of tissue. However, this safety standard of 1.6 W/kg was set 50 times stricter than the possible expected hazard level.

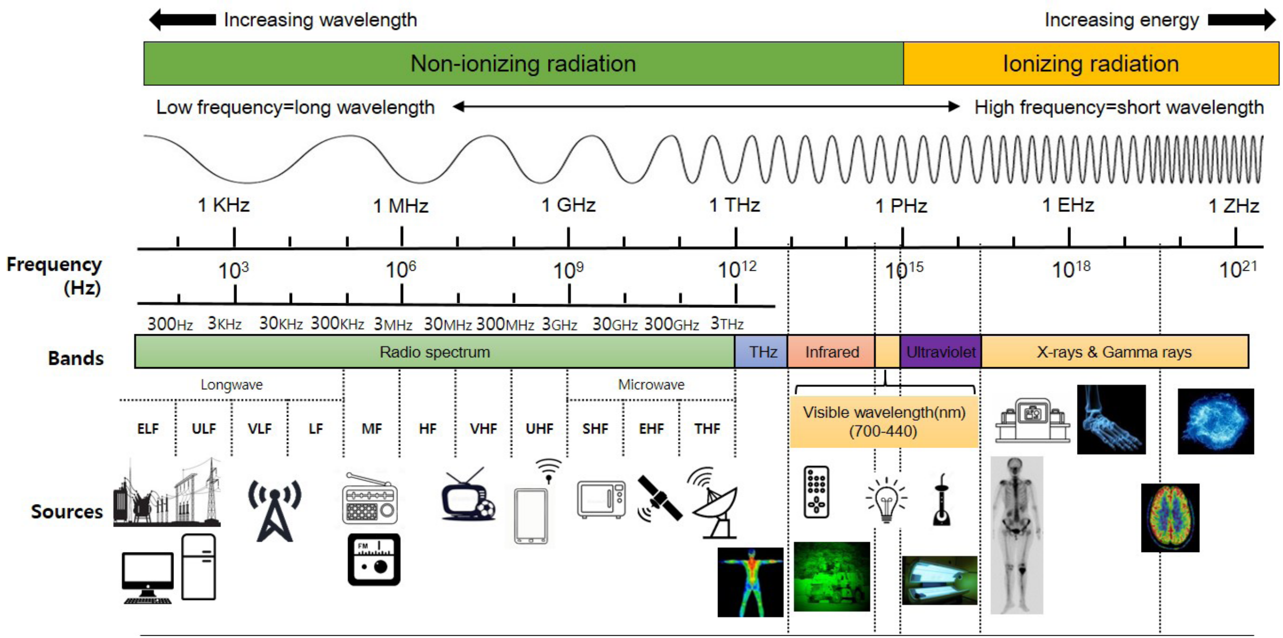

Fig. 2. Schematic illustration of spectrum of electromagnetic field in our environment.

EFFECTS OF EMF ON CANCER

Previously, epidemiological studies have been done whether children with chronic exposure to ELF-EMF or RF-EMF develop childhood leukemia and in adults, brain tumors and leukemia may occur (Lagiou *et al*., 2002; Swerdlow *et al*., 2011). Although there were some uncertainties, both epidemiological studies found that there is unlikely to be a material increase in risk of adult brain tumors or childhood leukemia resulting from the exposure to either ELF-EMF or RF-EMF. In addition, other studies have not found a direct evidence for the increase in the incidence of childhood leukemia due to ELF-EMF exposure (Kleinerman *et al*., 1997; Leitgeb, 2011; Jirik *et al*., 2012). Moreover, there is no direct correlation between acute lymphoblastic leukemia in children and exposure to ELF-EMF in the home (Kleinerman *et al*., 1997). Therefore, a standard health risk assessment process, the WHO Task Group of scientific experts concluded that there are no substantive health issues related to ELF-EMFs at levels generally encountered by members of the public.

However, it has been hypothesized that a variety of neurological influences may arise as a result of EMF exposure due to the location of the cellular phone and the proximity of the cranial nervous system. Therefore, a lot of concern is focused on possible carcinogenesis of the cranial nervous system by exposure to RF-EMF (Hardell *et al*., 2005). An epidemiological study claimed that using cell phones for one hour a day for more than 10 years could increase the risk of tumors (Hardell *et al*., 2007). In addition, cell phone users have an increased risk of malignant gliomas, particularly those with acoustic neuromas. Moreover, many studies have reported associations between RF-EMF and brain tumors (Myung *et al*., 2009; Swerdlow *et al*., 2011; Repacholi *et al*., 2012). In contrast, there are some studies claiming no association between brain cancer and cell phone usage (Benson *et al*., 2013) or due to nearby cellular base stations (Stewart *et al*., 2012). Another study showed that there was also no association between cancer and infants' risk of exposure to cellular base stations during pregnancy (Elliott *et al*., 2010). From this point of view, the observed results to date suggest that the association between the possible carcinogenicity of EMF and the cranial nervous system is complicated by a wide range of confounding variables. There is no clear evidence to support the causal relationship between increased carcinogenicity following exposure to EMFs (Moulder *et al*., 2005). Despite these controversies, the World Health Organization has classified RF-EMFs as 'possibly carcinogenic to humans' (Baan *et al*., 2011). However, the classification of RF-EMFs as possible carcinogens has yet to come to a clear conclusion among scientists. This is due to the fact that only 30 years have passed since the mobile phone has been used in earnest, it needs decades of exposure, and further epidemiological analysis to come to any conclusions.

GENOTOXIC EFFECTS OF EMF

There is considerable evidence that exposure to RF-EMF could cause various types of genotoxic effects in cells (Lai and Singh, 2004; Lee *et al*., 2005; Phillips *et al*., 2009; Ruediger, 2009; Xu *et al*., 2010). Exposure to RF-EMFs (1,800 MHz, SAR 2 W/kg) caused DNA oxidative damage in the mitochondria, DNA fragmentation and DNA strand breaks in neurons (Xu *et al*., 2010). This have been reported in lymphocytes exposed to various ranges of RF-EMFs (Phillips *et al*., 2009). In addition, RF-EMF exposure has been reported to cause chromosomal instability, alteration of gene expression and gene mutations. Such genetic toxic effects have been reported in, but are not limited to, neurons, blood lymphocytes, sperm, red blood cells, epithelial cells, hematopoietic tissue, lung cells and bone marrow (Magras and Xenos, 1997; Mashevich *et al*., 2003; Demsia *et al*., 2004; Zhao *et al*., 2007; Baan *et al*., 2011). It has also been found that exposure to electromagnetic radiation, a type of RF-EMF, increases the incidence of chromosomal aneuploidy (Mashevich *et al*., 2003). Genetic toxic effects, including aneuploidy, can lead to genetic disorders with abnormal gene formation, and can even lead to cancer (Hoeijmakers, 2009).

EFFECTS OF EMF ON THE BLOOD-BRAIN BARRIER

When rats were exposed to 900 MHz RF-EMFs, it was found that albumin leaks via the blood-brain barrier (BBB) (Salford *et al*., 1994, 2003, 2008; Nittby *et al*., 2009). However, the leakages via the BBB were not observed in studies by using rat or *in vitro* studies (Franke *et al*., 2005; Kuribayashi *et al*., 2005). Interestingly, neuronal damage in the cortex, hippocampus, and basal ganglia was significantly increased in a rodent model exposed to RF-EMFs (Salford *et al*., 2003). In previous studies related to stress and anxiety, exposure to RF-EMF has been reported to induce stress (Ray and Behari, 1990; Millan, 2003; Bouji *et al*., 2016) which can interfere with spatial memory performance (Micheau and Van Marrewijk, 1999). It was also examined the effects of microwave EMFs on benzodiazepine receptors related to stress and anxiety in the brain of rats (Lai *et al*., 1992) and found that these receptors were increased in the cortex (Millan, 2003). The change in BBB permeability in rats was reported to be due to signal-induced hyperthermia at 2.45 GHz, RF-EMF exposure (Sutton and Carroll, 1979). It has been shown that not only the continuous but also the pulsed wave (1.3 GHz, 3.0 mW/cm2) can increase the permeability of the BBB (Oscar and Hawkins, 1977). D'Andrea *et al*. (2003) and Stam (2010) summarized studies that affect the permeability of the BBB and suggested that exposure to RF-EMF may alter BBB properties. However, the authors emphasized that alterations in BBB permeation may be dependent on SAR (W/kg) (D'Andrea *et al*., 2003). In other words, if the signal intensity is sufficiently high (high SAR), the exposure to RF-EMF can cause a rise in the cranial nervous system temperature and change the physical characteristics of the BBB, but BBB permeability remains unchanged at low SAR (D'Andrea *et al*., 2003). However, Fritze *et al*. (1997) and Salford *et al*. (1994) suggested that the permeability of the BBB increases even in the absence of thermal effects due to exposure to RF-EMFs. Due to these conflicting results, the issue of changes in BBB permeability due to exposure to RF-EMFs remains controversial (D'Andrea *et al*., 2003). To assess the effect of exposure to RF-EMFs on BBB permeability changes, mice were exposed to 2.45 GHz microwave (SAR 2 W/kg) for 45 min after administration of scopolamine methylbromide, a muscarinic antagonist, and then alterations in cognitive functions were assessed (Cosquer *et al*., 2005). Finally, Evans blue, which binds to serum albumin in the rat vein, was injected before and after exposure to investigate whether scopolamine methylbromide crosses the BBB. The hypothesis of this experiment is that if the RF-EMF can alter BBB permeability, scopolamine methylbromide can cross the BBB more than in animals that have not exposed to the RF-EMF, as a result, there will be a change in the animals' performance of the radial maze. After exposure to the electromagnetic waves (2.45 GHz, whole body SAR 2.0 W/kg, Brain SAR 3.0 W/kg) and administration of the drug, the rats were tested in a 12-way radial maze. However, no difference in maze performance was observed between the groups administered with the drug before and after exposure to the RF-EMF. It was concluded that the BBB permeability did not change under these experimental conditions. Evans blue from the blood vessels of the rats did not show staining of the parenchyma, which supported this conclusion (Cosquer *et al*., 2005). Other possible changes in the permeability of the BBB by RF-EMFs may be due to changes of blood pressure which has been shown to affect the permeability of the BBB (Al-Sarraf and Philip, 2003; Hossmann and Hermann, 2003). Therefore, comprehensive studies on the exposure of RF-EMFs and changes in blood pressure are required.

EFFECTS OF EMF ON LEARNING AND MEMORY

It has been hypothesized that various neurological effects may arise as a result of RF-EMF exposure due to the proximity of the cranial nervous system during cellular phone use. These neurological effects include headache (Frey, 1998), changes in sleep habits (Wagner *et al*., 1998; Danker-Hopfe *et al*., 2016), changes in electroencephalogram (Mann *et al*., 1998; Schmid *et al*., 2012), and changes in blood pressure (Braune *et al*., 1998) but there are many inconsistent results. Neurological cognitive disorders, such as headache, tremor, dizziness, loss of memory, loss of concentration and sleep disturbance due to RF-EMF have also been reported by several epidemiological studies (Kolodynski and Kolodynska, 1996; Santini *et al*., 2002; Hutter *et al*., 2006; Abdel-Rassoul *et al*., 2007). The exposure levels of RF-EMF, commonly encountered in public environments have been found to be non-detrimental level to human (Repacholi *et al*., 2012), however with respect to the amount of exposure to RF-EMFs on the cranial nervous systems, a significant amount of research has focused on rodent behavioral disorders, particularly learning and memory deficits, after RF-EMF exposure under various conditions.

The radial maze and Morris water maze test showed that learning and memory functions were reduced in rats exposed to 2,450 MHz EMF (Lai *et al*., 1994; Wang and Lai, 2000), but no changes of working memory were observed in the radial maze test following whole body exposure for 45 minutes for 10 days at 2,450 MHz, 0.6 W/kg SAR (Cassel *et al*., 2004; Cobb *et al*., 2004) and in the Y-maze, Morris water maze, and novel object recognition memory test after exposed to 1950 MHz electromagnetic fields (SAR 5 W/kg, 2 h/day, 5 days/week) for 3 months (Son *et al*., 2016). Recognition memory was studied using the object recognition test (Mortazavi *et al*., 2014) using a head-only exposed mouse (900 MHz GSM, 1 and 3.5 W/kg SAR). In this study, there was no effect on learning and memory at low SAR levels, but at high SAR levels, only some of the exploration activities were changed (Dubreuil *et al*., 2002, 2003). Although exposure to RF-EMFs could affect cognitive function such as spatial learning and memory loss in both humans (Hossmann and Hermann, 2003; Preece *et al*., 1999) and in animals (Yamaguchi *et al*., 2003), direct evidence for the effects of RF-EMFs on these functions remains unclear (Ammari *et al*., 2008). The hippocampus is involved in spatial memory and learning processes (Morris *et al*., 1982; Moser *et al*., 1998) and low-intensity RF-EMFs at 700 MHz can alter electrical activity in hippocampal slices of the rat brain (Tattersall *et al*., 2001). Similarly, exposure to 1,800 MHz (15 min per day for 8 days, SAR 2.40 W/kg) has been reported to reduce excitatory synaptic activity of cultured hippocampal neurons (Xu *et al*., 2006). Although the water maze test results showed increased behavioral performance, there were no changes in spatial memory performances shown by both the open field or the plus maze tests, as well as in acoustic startle experiments in juvenile rats exposed to a 900 MHz for 5 weeks (2 hours per day, 5 days per week, SAR 3 W/kg) (Kumlin *et al*., 2007).

Recently, with regard to the effect of RF-EMFs on cognitive function, it has been found that exposure induced the improvement in cognitive behavior of triple transgenic mice (3xTg-AD), that have a cognitive impairment such as in human Alzheimer's disease (Banaceur *et al*., 2013). This experiment was performed with a Wi-Fi type, 2.40 GHz RF signal for 2 hours a day for 1 month at 1.60 W/kg SAR. Experimental results suggest that exposure of RF-EMF can lead to effective memory recovery in cognitive impairment in an experimental animal with loss of cognitive function caused by Alzheimer's disease (Banaceur *et al*., 2013). Despite numerous studies, it remains unclear if RF-EMF exposure is a risk for cognitive function, including memory. However, transgenic Alzheimer's mice with long-term RF-EMF exposure for more than 8 months have been reported to improve cognitive abilities (Arendash *et al*., 2010; Son *et al*., 2018). These series of experimental results suggest that exposure to RF-EMFs can improve memory in Alzheimer's disease, which is based on reduced response time, less anxiety, but no effect on exercise activity, body weight or body temperature (Arendash *et al*., 2010; Banaceur *et al*., 2013).

THERMAL EFFECTS OF EMF EXPOSURE TO BRAIN

Electromagnetic waves, particularly RF-EMFs emitted by mobile phones are absorbed into the brain to such an extent that it can affect the activity of neurons (Kleinlogel *et al*., 2008; Hinrikus *et al*., 2018). Research by the National Institutes of Health has reported that RF-EMFs emitted from mobile phones activates metabolic processes in the human brain (Volkow *et al*., 2011). RF-EMFs from cellular phones (837.5 MHz) were exposed to 47 healthy human's ears for 50 minutes, then, immediately after injection of 18F fluorodeoxyglucose, changes in brain metabolism were visualized by a positron emission tomography scan. Glucose metabolism in the brains that were exposed to RF-EMF increased rapidly. This provided evidence that the brain is sensitive to the effects of RF-EMF exposure (Volkow *et al*., 2011; Son *et al*., 2018). The thermal effects of RF-EMFs suggest the possibility of affecting neuronal activity by temperature generated by mobile phones (Wainwright, 2000). The established thermal effects of microwave radiation are heat generation by the rotation of polar molecules induced by RF-EMF. Some degree of temperature elevation can be lowered partially by blood circulation in the brain, but tissues such as the human eye, particularly the cornea, can be dangerous because there is no thermoregulatory system through blood circulation. For example, when rabbit eyes were exposed to 2,450 MHz (100-140 W/kg, SAR) for 30 minutes, the lens was elevated to 41°C, leading to cataract (Elder, 2003). However, cataract was not induced in experiments using monkeys under the same conditions. Of course, although the SAR of the RF-EMFs used in this experiment were set to be excessively high beyond the allowable limit, this does not exclude the possibility that RF-EMFs may cause eye diseases such as cataracts in humans using cellular phones regularly for a long period of time (Elder, 2003). Further research on the biological mechanisms and related medical symptoms is needed (Pall, 2015).

EFFECTS OF EMF ON NEURONAL CALCIUM CHANNELS

In addition to changes in genes, proteins, and proliferation in nerve cells exposed to RF-EMF, physiological changes in cell membranes and ion channels at cellular levels have been reported (Pall, 2013; Buckner *et al*., 2015). Changes in cell membranes and ion channels induce alterations in the electrical activity of neurons, and these changes stimulate or inhibit neuronal activity through interaction with voltage-gated ion channels (Nanou and Catterall, 2018). The electrical activity of ion channels plays an important role in the release of synaptic vesicles at the nerve terminal, which may also affect the release and reabsorption of synaptic vesicles in the neuronal membrane (Pchitskaya *et al*., 2018). In particular, calcium ion channels play an important role in regulating a variety of neuronal activities, including nerve cell excitation, neurotransmitter release, and neuronal synaptic plasticity (Neher and Sakaba, 2008). Calcium migrates into the cytosol through calcium channels according to neuronal activity, and then, binds to various calcium proteins in the cytosol which are used for physiological signaling of the cells. It has long been proposed that calcium, a key mediator of intracellular signaling and also an important factor in determining cell fate, is influenced by electromagnetic fields. Recently, ELF-MEFs have been reported to increase the expression of presynaptic calcium channels in the presynaptic terminal which promotes the release of synaptic vesicles (Sun *et al*., 2016). In particular, P/Q-type and N-type calcium channels were significantly increased by ELF-EMFs. They significantly increased the frequency of excitatory currents and accelerated synaptic vesicle release at the presynaptic terminal (Sun *et al*., 2016). However, the calcium-ion channels measured in the hippocampus of mice exposed to 835 MHz RF-EMF were significantly reduced (Kim *et al*., 2018a). Furthermore, the number and size of synaptic vesicles were significantly decreased in the cerebral cortex of mice exposed to RF-EMF (Kim *et al*., 2017a). Also, it has been reported that significant changes in excitatory current and frequency in neurons can cause significant neurophysiological changes in the mouse model (Aldad *et al*., 2012). T-type calcium channels, expressed in HEK293 cells, were suppressed by increasing arachidonic acid and leukotriene E4 after exposure of an ELF-EMF (Cui *et al*., 2014). These results suggest that the EMFs can indirectly control the intracellular signal transduction system which regulates the channel function in addition to directly affecting the regulation of intracellular calcium channel expression. It has also been suggested that ELF-EMF exposure (50 Hz, 1 mT) of embryonic neural stem cells may induce neural differentiation and neurogenesis by increasing the expression of transient receptor potential channel 1 together with an increase in intracellular calcium concentration (Ma *et al*., 2016). Neonatal mice exposed to RF-EMFs during pregnancy showed significantly decreased memory, but increased behavioral activities. These changes suggest the possibility of hyperactivity disorder and memory impairment in exposed mice during the early stages of development (Aldad *et al*., 2012). Although there is no direct evidence that these results from experimental animals show the same results in humans, exposure to RF-EMFs can cause changes in the expression and activity of ion channels, particularly in children. Further follow-up studies are needed to clarify the exact correlation with the changes in the expression and the activity of ion channels in neurons (Birks *et al*., 2017, 2018).

EFFECTS OF EMF ON MYELIN SHEATH

The Schwann cell, a glial cell, forms a myelin sheath, enclosing an axon of a peripheral neuron, which play a role as an insulator of axon fiber. The myelin sheaths form a spiral-like structure surrounding axons and are essential for the survival of neurons (Bhatheja and Field, 2006). Because it plays a key role in maintaining the survival of nerve cells, damage to the myelin sheath leads to demyelinating diseases such as chronic inflammatory demyelinate polyneuropathy. Demyelination could induce conduction velocity reduction, action potential dispersion and conduction block, and eventually cause axonal damage. Thus, the state of the myelin sheath is very important in the development and function of a healthy nervous system (Redmayne and Johansson, 2014). Exposure to RF-EMFs can cause significant structural changes in the myelin protein, affecting the proteins associated with myelinogenesis, leading to symptoms of electro-hypersensitivity (Redmayne and Johansson, 2014; Kim *et al*., 2017b). The inflammatory mediators, histamine and nitrogen peroxide were suggested as biomarkers that can measure electro-hypersensitivity. Also, nitrotyrosine, an indicator of the opening of the blood brain barrier, Protein S100B, and circulating autoantibodies against O-myelin were proposed as biomarkers of electo-hypersensitivity. An increased Hsp27 and Hsp70 expression were observed in animal experiments (Belpomme *et al*., 2015). The elevation of these factors could cause myelin sheath damage. In addition, early exposure to RF-EMFs increased malondialdehyde and glutathione levels, atrophy and vacuolization of spinal cord, and hypertrophy and irregularization of myelin in the cell body were observed, thus, leading to significant damage to the myelin sheaths and penetration into the axon (İkinci *et al*., 2016). Therefore, it is suggested that exposure of RF-EMFs may cause biochemical and pathological changes in the spinal cord.

Interestingly, it has been claimed that the symptoms of electro-hypersensitivity due to exposure to RF-EMFs can occur via oligodendrocyte, which plays an important role in myelin formation, much like the neuropathy caused by West Nile virus (Johansson and Redmayne, 2016). Furthermore, it has been proposed as a possible mechanism of neuronal damage and dysfunction due to astrogliosis following exposure to RF-EMFs through observation of glial fibrillary acidic protein (GFAP) increase in the nervous system. In addition, acute exposure of RF-EMFs is suggested as a possible mechanism of neuronal damage and dysfunction. This is due to astrogliosis as a result of exposure to electromagnetic waves observed by GFAP increase in the nervous system (Barthélémy *et al*., 2016). However, contrary to previous reports, it has been suggested that electromagnetic stimulation may enhance the proliferation and migration of subventricular neural stem cells, thereby reducing the extent of demyelination and promoting remyelination (Sherafat *et al*., 2012). In neurological diseases, transcranial magnetic stimulation has been shown to improve paralysis and decrease cellular damage due to oxidative stress and to increase antioxidant activity (Medina-Fernandez *et al*., 2017). These results suggest that there is a possibility of reducing nerve damage in addition to the induction of RF-EMFs damage to the myelin sheath. Therefore, further study is needed to clarify the influence of RF-EMFs on myelin sheaths.

EFFECTS OF EMF ON AUTOPHAGIC ACTIVITIES IN NEURON

Autophagy plays a role in eliminating intracellular damage or aged cellular organelles and aggregated, unnecessary proteins in cells. Autophagy consists of a series of cytoprotective mechanisms essential for cell survival and homeostasis. Thus, the activation of autophagy is always occurring in our body to maintain a healthy state and is rapidly and efficiently activated in various stress situations (Nixon, 2013; Feng *et al*., 2014; Fujimoto *et al*., 2017). In cellular and animal models exposed to RF-EMF, the activation of autophagy is of great interest, but very limited results were reported so far. A recent study has shown that 55 healthy male Sprague Dawley rats continuously exposed to electromagnetic pulses (EMP; 100, 1,000-10,000 pulses, field strength 50 kV/m and frequency 100 Hz), showed significantly increased expression of LC3-II, a key protein of autophagy, in the hippocampus which is an important brain region for memory and learning (Jiang *et al*., 2016). In addition, studies using human neuroblastoma cells (SH-SY5Y) showed that LC3B-II, Beclin 1, and ATG7, which are major factors of autophagy activation, were significantly increased after exposure to ELF-EMF. Also, LC3B was activated, and autophagosomes and phagophore-like structures with a double-membrane were found in the cells (Marchesi *et al*., 2014). The longer the reaction time after exposure to EMF, the higher the activity of the autophagy. Recently, we have reported that autophagy is activated in nerve cells of mice exposed to 835 MHz RF-EMF for 4-12 weeks. The expression of autophagy related proteins such as AMPK1α, Ulk1, Atg4/B, Beclin1/2, Atg5, Atg9A, and LC3A/B were significantly increased in the cerebral cortex of mice, and LC3B-II also showed high activity (Kim *et al*., 2017b). Also, it was found that the activation of autophagy in the striatum and hypothalamus of RF-EMF exposed mice (Kim *et al*., 2016), and p62, another autophagy related protein, was activated by exposure to RF-EMF in the hippocampus (Kim *et al*., 2018b). However, there was a difference in the degree of autophagic activities between the brain regions of the mice, in particular, autophagic activity was very low or not active in the region of the brainstem. It is presumed that the response to electromagnetic stress is different for each brain region. The autophagosome and autolysosome, which are major autophagic structures, were increased 3-4 times higher than in the control group (Kim *et al*., 2018b). These results suggest that the activation of autophagy could be one of the main adaptation mechanism of neurons to electromagnetic stress.

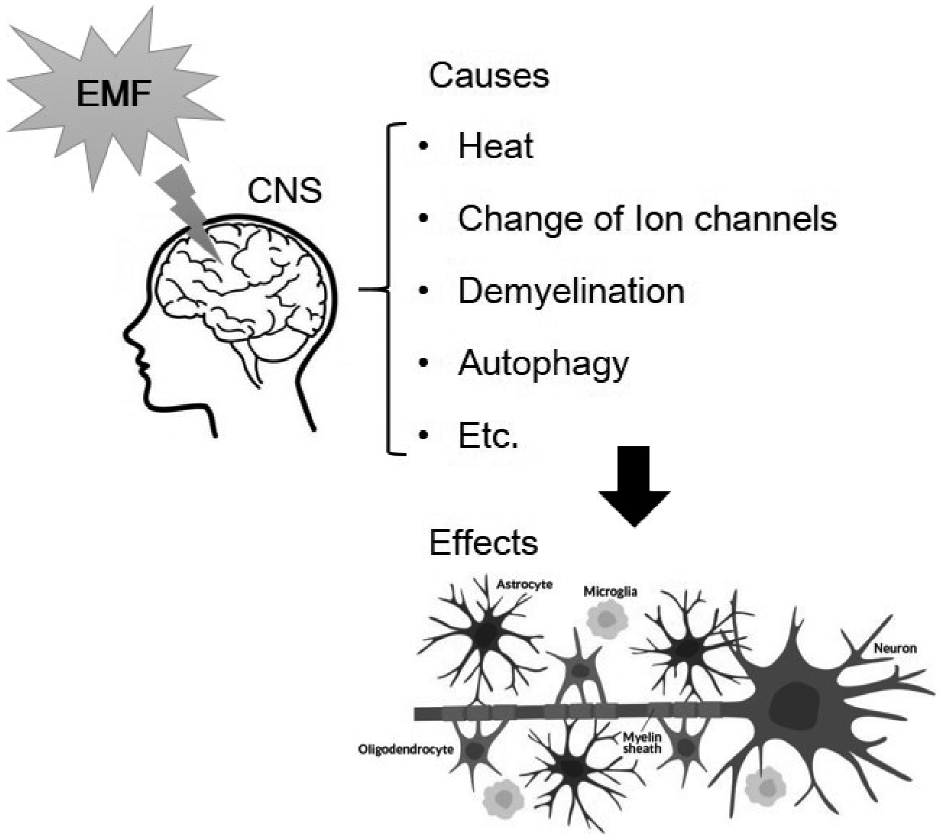

Fig. 3. Schematic summary of the possible mechanisms of RF-EMF exposure in central nerve system.

SUMMARY AND CONCLUSION

Human beings have developed communication technology along with the development of numerous electronic products in accordance with scientific and technological progresses. Due to these technological developments, the demand for usage of various electronic devices to maintain modern society is continuously increasing, especially the development of wireless communication technologies such as smart phones, which have become a necessity for modern people. In addition, the frequency ranges are continuously widening due to various types of electronic devices are being used. Because mankind uses any electronic devices, electromagnetic fields are generated essentially. Some equipment used in broadcast, communications and transportations also liberated electromagnetic waves to the entire communities. When using any electronic devices, essentially electromagnetic waves are generated. These waves can be absorbed by human or animal bodies, even despite the unintended. Among various electronic devices, smart phones are used close to our body, and the use time has been rapidly increasing recently. Moreover, the use of smartphones has increased not only in adulthood, but also in youth and elderly people including young children. Therefore, there are increasing concerns about the possible biological effects of electromagnetic fields liberated from electronic devices including smart phones. However, there is a lack of information on the possible effects of artificial electromagnetic fields on living organisms liberated from the use of such devices and equipment.

The IARC has classified RF-EMFs as a possibly carcinogenic to humans (Baan *et al*., 2011) and warms of the danger of EMF exposure. Moreover, it has been hypothesized that a variety of neurological effects may occur as a result of RF-EMF exposure due to the proximity of the cranial nervous system and the location where the cellular phone is predominantly used. These neurological abnormalities include headache (Frey, 1998), changes in sleep habits (Wagner *et al*., 1998), and changes in EEG (Braune *et al*., 1998; Mann *et al*., 1998). In addition, significant statistical results have been reported by various epidemiological studies on neurological cognitive disorders such as headache, tremor, dizziness, memory loss, loss of concentration, and sleep disturbance due to RF-EMF (Kolodynski and Kolodynska, 1996; Santini *et al*., 2002; Hutter *et al*., 2006; Abdel-Rassoul *et al*., 2007). As a possible mechanism for the change of neurological functions by RF-EMFs exposure, we are confident that more mechanisms will be involved than those mentioned, but we have summarized only recent studies on thermal effects, activation of autophagy processes, changes in ion-channel expression, and changes in myelin sheaths in this review (Fig. 3). Most of these studies were performed using cell or animal models and they have provided basic information on the underlying possible biological effects of RF-EMFs exposure to living creatures. So, these results could not apply to humans directly. Precise epidemiological studies are needed to confirm the possible biological effects of RF-EMF exposure to humans. Recently, the governmental regulation on RF-EMFs of individual devices has been introduced to reflect the concern about the biological effect of RF-EMFs. However, the possible biological effects on electromagnetic fields exposure has not yet been well established even in scientific communities. Therefore, it is necessary to apply international standard at the preventive level at least and disclose related information to public in a transparent manner.

CONFLICT OF INTEREST

The authors declare no competing interests.

ACKNOWLEDGMENTS

This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, Ministry of Science, ICT, and Future Planning (NRF-2014R1A2A2A04003616) and by the Ministry of Education (NRF-2017R1D1A1B03029527).

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